

MANAGEMENT OF METABOLIC SYNDROME POST LIVER TRANSPLANT (LT)

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IN THE NEXT 20-
25 MINUTES....

Case presentation

Obesity pre LT

Obesity post LT

Metabolic dysfunction-Associated Steatotic
Liver Disease (MASLD)

- Post LT diabetes (DM)
- Post LT hypertension (HT)
- Post LT dyslipidaemia

CASE

52, female, originally from Tonga

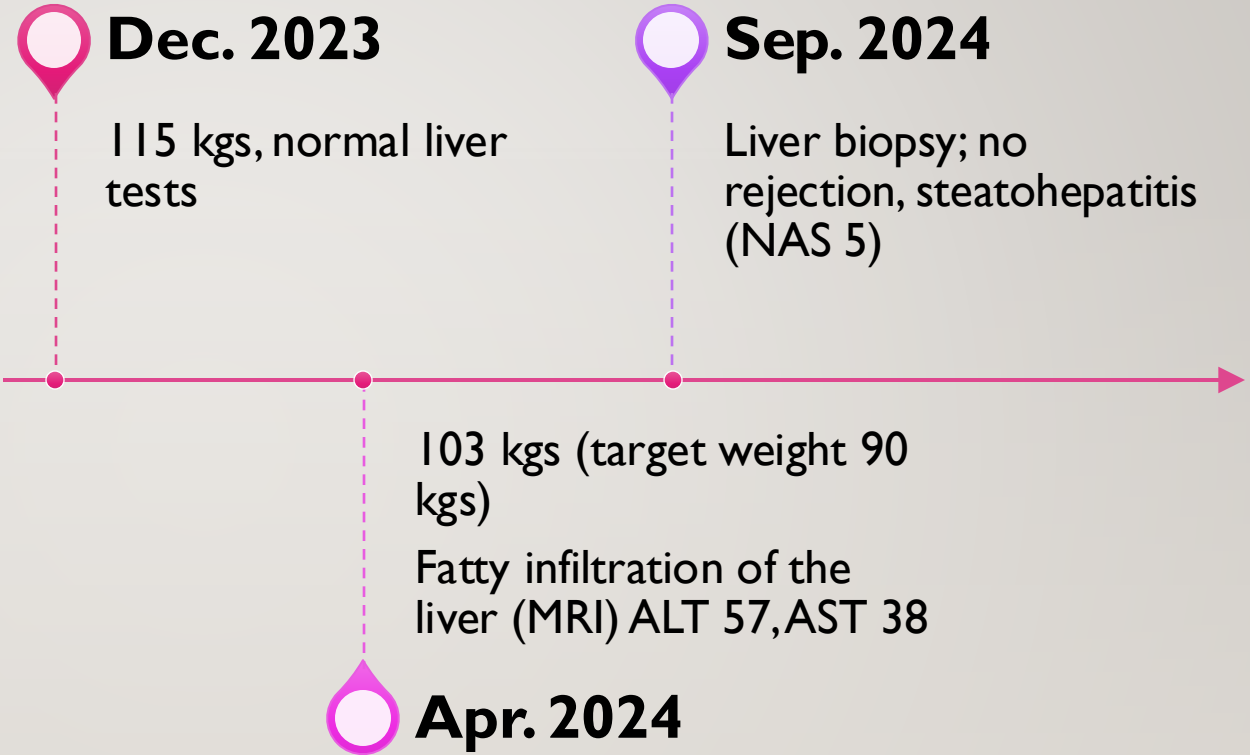
Transferred November 2023
for consideration of LT

- MELD 31, CPS C12 (flare of hepatitis B)
- MASLD (US 2023)
 - BMI 51
 - DM; novorapid, optisulin; HbA1c 4.7% (28 mmol/mol)

LT 30/11/2023, discharged
11/12/2023

- Steroid sparing regimen
- Discharge weight 138 kgs

CASE



CASE

- Now
 - AST 43,ALT 63, GGT 102
 - BMI
 - 42.4
 - Cholesterol 5.8,TG 2.5, LDL 3.2, non-HDL 4.3
 - Rosuvastatin 20 mg
 - BP 130/85
 - Amlodipine 10 mg
 - HbA1c 8.6%; 70 mmol/mol
 - Metformin
 - Semaglutide 0.25 mg/weekly, plan to titrate
 - Glargine, insulin

OBESITY PRE-LT

- No longer a contraindication (CI) to LT
 - BMI > 40 is a relative or absolute CI?
- MASLD = second leading indication for listing
- MASLD = third leading indication for transplant
- Post transplant obesity
 - DM, metabolic syndrome, OSA, cardiovascular
 - Immunosuppression amplifies these risks
- Management is crucial as soon as LT is considered

OBESITY PRE LT

- What can we do?
 - Diet
 - Exercise
 - Anti obesity medications
 - Surgery

OBESITY PRE LT

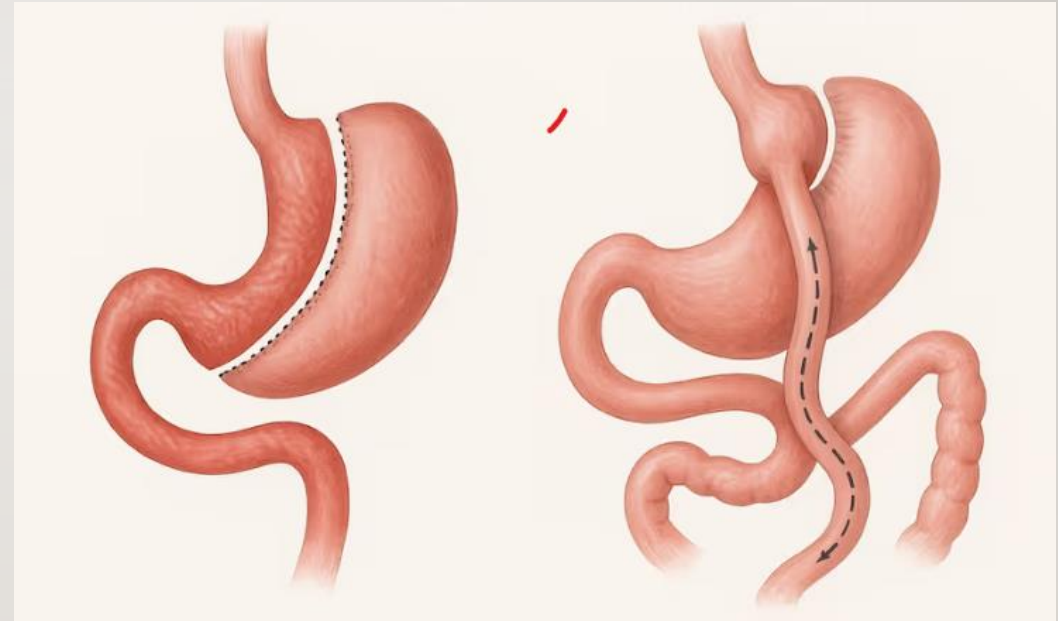
- Part of prehabilitation in some LT units (diet and exercise)
- Mayo clinic
- BMI ≥ 35 listed for LT
- 74 patients
 - 45 managed to get to a lower BMI than 35 - LT
 - 29 didn't – LT and SG
- Amount of weight gain was higher in LT only; lower starting BMI in LT only group (40 vs 47.8)

OBESITY PRE LT

- GLP-1 receptor agonists (GLP-1 RA) e.g semaglutide
 - 1961 patients with BMI ≥ 30 (≥ 27 with 1 or more weight related condition)
 - Semaglutide vs placebo and lifestyle intervention
 - Mean change in body weight from baseline to week 68 was -14.9% with semaglutide compared with -2.4%
 - Sustained body weight reduction
- Wilding et al. NEJM 2021; 384: 989-1002

OBESITY PRE LT

- Weight loss surgery
 - Before?
 - During?
 - After?
- What method?



OBESITY PRE LT

- Prior to LT
 - 10 published studies (285 patients)
 - History of weight loss surgery, then became candidates for transplant
 - Scheduled during pre-LT work up phase
 - Average excess body weight loss at 1y post surgery @ 30%, maintained at 1 year post LT
- EASL CPG on liver transplant. Journal of Hepatology Dec 2024. vol 81, 1040-1086

OBESITY PRE LT

- During LT?
 - 6 studies published
 - Maintenance of weight loss demonstrated
 - Decrease in metabolic, cardiovascular risk factors; identical survival compared to those who didn't have a SG

OBESITY POST LT

- BMI prior to and following LT is a major risk factor for post LT MASLD
- Recurrent or de novo?
- Counselling
 - Diabetes
 - Graft steatosis
 - Malignancy
- New onset overweight or obesity within 24m of LT is reported in 36% of recipients
- Martinez-Camacho et al. European Journal of Gastroenterology Hepatology 2016; 28 (1): 107-115

OBESITY POST LT

- 327 patients over 5 years
 - When does the weight gain start?
- Only 12.5% had MASLD as primary liver disease
- Weight increase of 4.2% observed at 12m following LT
- Initial weight loss 0-8 weeks
- Significant weight gain at 8-13 weeks
- Early intervention

OBESITY POST LT

- GLP-1 RA?

- Promising data but need to be confirmed in larger cohorts with longer FU periods
- 2 retrospective studies
 - 23; 70% had DM; mean time between LT and starting 136 months
 - 0.25-2mg; 17 months FU; 87 kg vs 92 kg ($p < 0.01$) which is only 5.4%
 - Chow et al. Liver Transplantation 30 (2): 223-225 February 2024
- 44 patients started on anti obesity medications, 75% GLP1-RA
- 7.87% of TBW compared to baseline ($p < 0.01$), 4.24% in non GLP-1 RA group
- Richardson et al. Liver Transplantation 30 (2): 226-228 February 2024

OBESITY POST LT

- Medium to long term
 - Case reports
 - 2 retrospective studies
 - 6m post LT; 15 patients; FU 2.6 years
 - BMI 42.7-35.9 ($p < 0.01$); reduced insulin or discontinued
 - Mackenzie et al. Liver Transplantation 25 (11); p1673-1681, November 2019
 - 36 patients
 - Change in BMI similar, resolution of comorbid conditions similar
 - Tsamalaidze et al. Obesity Surgery volume 28, p 444-450, 2018

OBESITY AND LT

- EASL
 - If compensated cirrhosis and BMI > 35 without clinically significant portal hypertension, consider weight loss surgery
 - If decompensated and BMI > 35, consider at the time of or after
 - SG > RYGB
 - (GLP-1RA)???

MASLD – POST LT

- Heterogenous definitions of disease recurrence
 - Specific follow up?
 - What type of screening?
 - How frequent?
 - When to biopsy the liver?
 - Donor liver?
 - Ideally, evaluate diet, alcohol use, physical activity in all
 - Higher risk for cardiovascular (CV) disease, malignancy, T2DM, chronic kidney disease (CKD)
 - No difference in 1y and 5y graft and patient survival after LT
- Zhou et al. Clinical evidence of outcomes following LT in patients with NASH; an updated meta-analysis and systematic review. Int J Surg. 2022; 104:106752

MASLD – POST LT

- Immunosuppression?
 - The use of corticosteroids beyond 3-6 months should be avoided in adult LT patients transplanted for MASLD due to a higher risk of post transplant DM and metabolic syndrome
 - Lowering calcineurin inhibitor exposure may be considered in adult LT recipients transplanted for MASLD +/- MMF
 - AASLD AST practice guideline on adult LT: diagnosis and management of graft related complications (in press)

FACTOR	CORTICOSTEROIDS	TACROLIMUS	CYCLOSPORINE	SIROLIMUS
Abdominal obesity	+	-	-	-
Dyslipidemia	+	+	+	+++
Systemic hypertension	+	++	++	+
Insulin-resistant DM	+++	++	+	-

- Long term management of adult liver transplant: 2012 Practice Guideline by AASLD and AST

MASLD – POST LT DM

- New onset DM seen more commonly with tacrolimus compared to cyclosporine
 - Increases with prolonged exposure
 - Trough cutoff for predicting new onset DM is 5.89 ng/ml
- Lower trough levels (3-5 ng/mL) +/- an alternative agent
- Follow guidelines of the general population

MASLD – POST LT DM

- Target HbA1c < 7%
- Tight control is important as diabetes:
 - Graft steatosis
 - Progression to fibrosis
 - Decreased patient and graft survival
- GLP-I RAs can be prescribed

- Russo et al. Management of long-term complications from immunosuppression. Liver Transplantation 2024; 30: 647-658

MASLD – POST LT DM

- What agent?
 - Safe and personalised
 - Consider
 - CKD
 - CV disease
 - Allograft steatosis
 - Obesity
 - De novo malignancy
 - Some agents can benefit, some can cause more harm
 - Challenging but can have overlapping benefits (CV disease, obesity)

REVIEW | HEPATOLOGY COMMUNICATIONS, VOL. 6, NO. 6, 2022

Personalizing Diabetes Management in Liver Transplant Recipients: The New Era for Optimizing Risk Management

MASLD – POST LT DIABETES

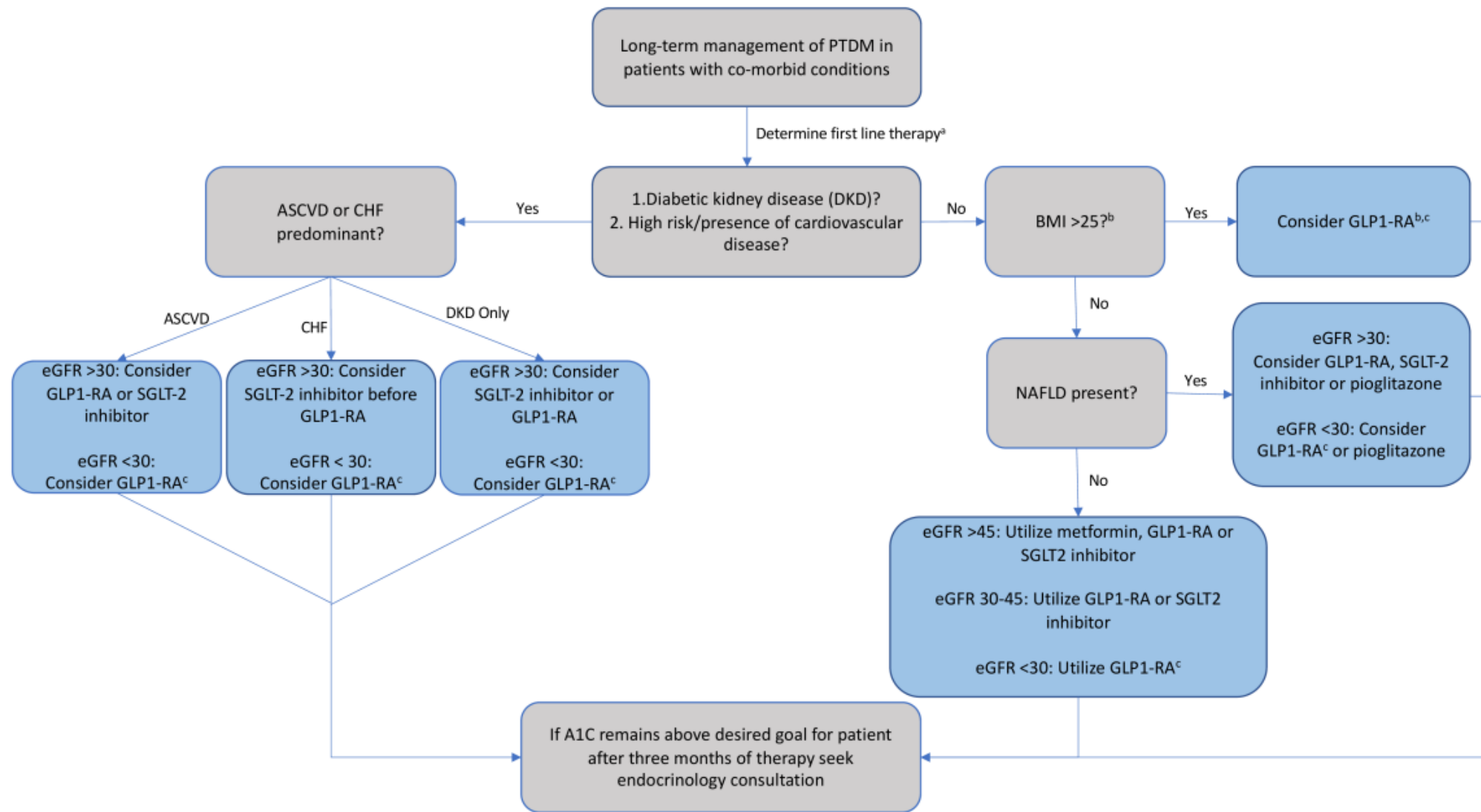


MASLD – POST LT DM

- Do they have diabetic kidney disease?
 - 25% of LT recipients develop stage 4-5 chronic kidney disease (CKD) within 5 years following LT
 - T2DM is a risk factor
 - Sodium-Glucose Co-Transporter-2 inhibitors (SGLT2i) are contraindicated in end stage kidney disease (ESKD) but demonstrated benefit in terms of progression of renal disease
 - GLPI-RAs reduce adverse renal outcomes including new onset macroalbuminuria, decline in glomerular filtration rate (GFR), progression to ESKD and death

MASLD – POST LT DIABETES

- Do they have high risk or presence of cardiovascular death?
 - LT recipients have a 30.8% risk of cardiovascular death within 8 years following LT
 - SGLT2i show significant reductions in the risk of CV death, congestive heart failure, reduction in systolic BP, increase in HDL, decrease in TG
 - GLPI-RAs reduce CV death, myocardial infarction and stroke
 - Lower weight, lower BP, lower triglyceride and anti-thrombotic effects



MASLD – POST LT DYSLIPIDAEMIA

- Up to 51% of patients can get this after LT
- Cyclosporin > tacrolimus
 - Increases LDL
- Systematic review in 2021, Singapore
 - 11 studies, 697 LT recipients; 32% taking a statin
 - In those taking statins, significant mortality benefit
 - Less rejection, less HCC recurrence
 - Safe!
- Ho et al. Transplantation 2021, 2(3), 264-273

MASLD – POST LT DYSLIPIDAEMIA

- Which one?
 - Simvastatin and atorvastatin metabolised by CYP450 3A4, like tacrolimus and cyclosporin so statin levels may increase
 - Risk of rhabdomyolysis
 - Rosuvastatin (pravastatin, fluvastatin, pitavastatin) are preferred
- Annual check (after a 14 hour fast)
- LDL > 2.6 mmol/L +/- raised TG
- ? ezetimibe
- Long term management of adult liver transplant: 2012 Practice Guideline by AASLD and AST

MASLD – POST LT DYSLIPIDAEMIA

- Isolated hypertriglyceridaemia (> 4.5 mmol/L) with omega-3 fatty acids is recommended
 - or fenofibrate
 - Long term management of adult liver transplant: 2012 Practice Guideline by AASLD and AST
- Higher rates with sirolimus/everolimus

MASLD – POST LT HT

- HT is the most common metabolic complication after LT
 - 70% of recipients
 - CNIs cause HT by increasing systemic vascular resistance and renovascular constriction
 - Cyclosporin > tacrolimus
 - Ca channel blockers
 - Amlodipine
 - +/- ACE/ARB (not in early post operative period due to risk of hyperkalaemia)
 - Target 130/80

IN CONCLUSION...

- Dramatic increase in patients with MASLD requiring a LT
 - Tend to be older
 - Higher BMI
 - More DM
- Identify risks pre liver transplant
- Optimise immunosuppression
- Prevent recurrent MASLD by preventing or managing metabolic syndrome components
- Further work on how to truly optimise the management of the liver allograft in terms of preventing MASLD

(and don't forget alcohol!)